in which the peptides are displayed on viruses.

REMARKS

1. Claim 27 has been amended to clarify the nature of the constant residues in the panel. Since a panel consists of a plurality of libraries, one can distinguish two kinds of "constant" residues:

(1) where, for all peptides in the entire panel, a particular amino acid position is constant (the same amino acid), and

(2) where, for all peptides in a given library, a particular amino acid position is constant, but that position is variable when viewed from the perspective of the entire panel.

Thus, the definition of "structured panel" at page 10, lines 1-8 says

> A "structural panel" is a panel as defined above where there is some structural relationship between the member libraries. For example, one could have a panel of 20 different biased peptide libraries where, in each library, the middle residue is held constant as a given amino acid, but, in each library the constant residue is different, so, collectively, all 20 possible genetically encoded amino acids are explored by the panel.

The "middle residue" of that passage is clearly a "constant residue" of the second kind.

At page 25, lines 25-32, the specification says:

> In one embodiment, an internal residue is constant, so that the peptide sequence may be written as
>
> $(X_{aa})_m$-AA_1-$(X_{aa})_n$
>
> Where Xaa is either any naturally occurring amino acid, or any amino acid except

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Received from < 2027373528 > at 6/10/03 2:32:24 PM [Eastern Daylight Time]

> cysteine, m and n are chosen independently from the range of 2 to 20, the Xaa may be the same or different, and AA_1 is the same naturally occurring amino acid for all peptides in the library but may be any amino acid.

A "structured panel" may be constructed using a plurality of these libraries, in which case, if AA_1 varies from library to library, it is a constant amino acid of the second kind. At page 26, lines 22-26 we contemplate a panel of 20 such libraries. However, we teach at page 26, L27 that we may instead screen a "subset" of these 20 libraries. In the Examples, we used structured panels which consisted of four (P58, L15-17) or ten (P71, L28-34) of these libraries, each panel having one constant residue of the second kind.

The specification also contemplates constant residues of the first kind. First of all, there may be a known binding motif for peptides which bind the target, in which case this may be used as a starting point. See P26, L30-P27, L8; P58, L18-20. Secondly, N- or C-terminal linkers may be used to improve the display of target binding site. (The C-terminal linker minimizes steric hindrance by the phage, and the N-terminal linker minimizes interference from an attached label, such as biotin.) Thus, at P96, L38-P97, L10, the libraries screened were of the form

$$SR\text{-}X_5UX_5\text{-}SR,$$

where the S and R are constant residues of the first kind, the U is a constant residue of the second kind, and the X are fully variable.

Likewise on pp. 110-112, we see use of both SS- and SR- as N-terminal linkers, and -SR as a C-terminal linker. Other linker moieties (such as GG, GSG and SGS) are suggested at P52, L30-38.

Thus, claim 27 has been amended to recite that there is one and only one position in the peptides of the panel which is both

Received from < 2027373528 > at 6/10/03 2:32:24 PM [Eastern Daylight Time]

(a) for each library, the same amino acid in all peptides of that library, and (b) not the same amino acid in all libraries of said panel. Thus the limitation to "one and only one" clearly applies now only to constant residues of the second kind.

2. In claims 32, 33 and 35, which relate to group II, we likewise acted out of concern that the term "constant residues" would not be limited to constant residues of the second time.

For these claims, we thought it easiest to change "exactly two" to "at least two", but with the caveat (after defining the first and second positions) that where if said libraries comprise more than two constant residue positions, the remaining constant residue positions are constant for all peptides in said panel, i.e., there are only two constant positions of the second kind; all others (if any) are of the first kind.

These claims have also been amended to provide that the scanning position (second position) need only scan a plurality of the residue positions. See P10, L14.

It should be noted that for this invention, there are two ways of defining subpanels. One is the method presently used, and derived from original claim 23, where, for all libraries of the subpanel, the scanning residue, whose identity varies from library to library of the subpanel, is in the same position (and its position varies from subpanel to subpanel). Another is suggested by P10, L17-20, that is, based on the identity of the AA in the first, fixed position. We use the first method in the claims.

New claims 39-42 address the constant residues of the first kind.

New claims 43-45 restore the excised limitation (32, 33, 35) as to which positions are scanned.

New claim 46 is based on amended 27, but allows for <u>one or two</u> residues of the second kind. Since the group II claims have two constant residues of second kind, 46 covers, not only all of

Received from < 2027373528 > at 6/10/03 2:32:24 PM [Eastern Daylight Time]

group I, but also some of group II (46, like 27 and unlike 32, 33 and 35, requires phage display).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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Received from < 2027373528 > at 6/10/03 2:32:24 PM [Eastern Daylight Time]

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 27, 32, 33, and 35 have been amended as follows:

27 (thrice amended). A structured panel consisting of a plurality of biased combinatorial linear peptide libraries, each library comprising a plurality of different peptides, all peptides of said panel being of the same length, [having] there being one and only position in said peptides which is both (1) for each library, the same amino acid (a "constant" amino acid) in all peptides of that library, and (b) not the same amino acid in all libraries of said panel, [one constant residue at a] said position being fixed for all peptides in all libraries of said panel, [all peptides of said panel being the same length,] wherein[, in each library,] said fixed position is (a) at least five residues from both ends of the peptides or (b) within the middle 50% of the peptides,

[wherein the amino acid is assigned to said fixed position is not the same in all libraries of said panel,]

each library being a separate and physically distinct entity from all other libraries of the panel,

in which the peptides are displayed on viruses.

32 (twice amended). A structured panel of biased combinatorial linear peptide libraries, each library comprising a plurality of different peptides, all peptides of said panel being the same length, each library having [exactly] at least two constant residue positions, one at a first position and the other at a second position,

where the first position is fixed for all libraries in the panel, and is assigned the same residue for all peptides in any given library, but libraries of the panel collectively present a plurality of different residues at said first position,

where said first position is (a) at least five amino acids

Received from < 2027373528 > at 6/10/03 2:32:24 PM [Eastern Daylight Time]

from both ends of the peptides, or (b) is in the middle 50% of the peptides,

where said panel comprises a plurality of subpanels, each comprising a plurality of libraries, and in each subpanel, the location of the second position is constant, but said location varies from subpanel to subpanel so the second positions of said subpanels, collectively scan [all] a plurality of residue positions [except for] other than said first position,

where the second position is assigned the same residue for all peptides in a given library but the libraries of a given subpanel collectively present a plurality of different residues at said second position,

where if said libraries comprise more than two constant residue positions, the constant residue positions other than said first and second positions are constant for all peptides in said panel,

where one or more of the other positions of said libraries are variable positions, at which a given library exhibits a plurality of different residues as a result of sequence variation from peptide to peptide,

each library being a separate and physically distinct entity from the other libraries of the panel.

33 (twice amended). A structured panel of biased combinatorial linear peptide libraries, each library comprising a plurality of different peptides, all peptides of said panel being the same length, each library having [exactly] at least two biased residue positions, one at a first position and [the other] another at a second position, the amino acids allowed in each library at said biased positions being only a subset of the set of amino acids allowed at the remaining positions of said library, and also being only a subset of the set of amino acids allowed at that biased position in the panel as a whole,

where the first position is fixed for all libraries in the

Received from < 2027373528 > at 6/10/03 2:32:24 PM [Eastern Daylight Time]

panel,

where said first position is (a) at least five amino acids from both ends of the peptides, or (b) is in the middle 50% of the peptides,

where said panel comprises a plurality of subpanels, each comprising a plurality of libraries, and in each subpanel, the location of the second position is constant, but said location varies from subpanel to subpanel so the second positions of said subpanels collectively scan [all] a plurality of residue positions [except for] other than said first position,

where if said libraries comprise more than two constant residue positions, the constant residue positions other than said first and second positions are constant for all peptides in said panel,

each library being a separate and physically distinct entity from the other libraries of the panel.

35 (twice amended). A structured panel of biased combinatorial linear peptide libraries, each library comprising a plurality of different peptides, all peptides of said panel being the same length, each library having [exactly] at least two biased residue positions, one at a first position and [the other] another at a second position, the amino acids allowed in each library at said biased positions being only a subset of the set amino acids allowed at the remaining positions of said library, and also being only a subset of the set of amino acids allowed at that biased position in the panel as a whole,

where the first position is fixed for all libraries in the panel,

where said first position is (a) at least five amino acids from both ends of the peptides, or (b) is in the middle 50% of the peptides,

where each library is obtained by mixing a plurality of different mixed oligonucleotides, each oligonucleotide comprising

Received from < 2027373528 > at 6/10/03 2:32:24 PM [Eastern Daylight Time]

one fully variable codon and one less variable codon, the position of the less variable codon varying so that said plurality collectively scan also positions other than said first fixed position, said less variable codon encoding the second position of each peptide,

where if said libraries comprise more than two constant residue positions, the constant residue positions other than said first and second positions are constant for all peptides in said panel,

each library being a separate and physically distinct entity from the other libraries of the panel.

Claims 39-46 have been added.

Received from < 2027373528 > at 6/10/03 2:32:24 PM [Eastern Daylight Time]